

Dose-Response: An International Journal

Volume 4 | Issue 1

Article 4

1-2006

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Irit Akirav

University of Haifa, Haifa, Israel

Gal Richter-Levin

University of Haifa, Haifa, Israel

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Recommended Citation

Akirav, Irit and Richter-Levin, Gal (2006) "FACTORS THAT DETERMINE THE NON-LINEAR AMYGDALA INFLUENCE ON HIPPOCAMPUS-DEPENDENT MEMORY," *Dose-Response: An International Journal*: Vol. 4 : Iss. 1 , Article 4.

Available at: https://scholarworks.umass.edu/dose_response/vol4/iss1/4

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Dose-Response, 4:22–37, 2006
Formerly *Nonlinearity in Biology, Toxicology, and Medicine*
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ISSN: 1559-3258
DOI: 10.2203/dose-response.004.01.003.Akirav



FACTORS THAT DETERMINE THE NON-LINEAR AMYGDALA INFLUENCE ON HIPPOCAMPUS-DEPENDENT MEMORY

Irit Akirav and Gal Richter-Levin □ Department of Psychology and The Interdisciplinary Research Center for Brain and Behavior, University of Haifa, Haifa 31905, Israel

□ Stressful experiences are known to either improve or impair hippocampal-dependent memory tasks and synaptic plasticity. These positive and negative effects of stress on the hippocampus have been largely documented, however little is known about the mechanism involved in the twofold influence of stress on hippocampal functioning and about what factors define an enhancing or inhibitory outcome. We have recently demonstrated that activation of the basolateral amygdala can produce a biphasic effect, enhancement or inhibition, of hippocampal synaptic plasticity, depending on the timing of activation (priming or spaced activation). A key question is under which conditions do the effects of amygdala activation on hippocampus dependent memory functions change from improvement to impairment of learning and memory. In this chapter we suggest that hippocampal outcome of amygdala activation may be critically dependent on four main factors: (1) The intensity of amygdala activation, (2) the temporal relation between the activation of the amygdala and the hippocampus dependent memory function, (3) the duration of amygdala activation, and (4) the contextual input during the processing of the information.

Keywords: Amygdala, Hippocampus, Plasticity, Stress.

A. EMOTIONALLY AROUSING EVENTS ARE MEDIATED BY THE AMYGDALA IN AN INVERTED U-SHAPED FUNCTION

Emotional states range from positive to negative, and both can range from low to high levels of arousal. Research in the field of emotional memories usually focuses on the negative end of emotional experiences due to the profound neurobiological effects of stressful experiences on learning and memory. These effects are believed to be the basis of many cognitive and affective changes in health and disease (McEwen and Sapolsky, 1995).

The amygdala is an important brain structure for the recognition of negative, unpleasant emotions, such as fear, and for associating environmental stimuli with emotionally charged, aversive sensory inputs. Most of the evidence points to the basolateral amygdala nucleus (BLA; comprised of the lateral, basal, and accessory basal nuclei) as particularly important in the acquisition, consolidation, and retrieval of emotional information

Address correspondence to Gal Richter-Levin, Department of Psychology and The Interdisciplinary Research Center for Brain and Behavior, University of Haifa, Haifa 31905, Israel. Tel: 972-4-8240962; Fax: 972-4-8288578; e-mail: gal.r-l@psy.haifa.ac.il.

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(Cahill and McGaugh, 1998; Davis, 1992; Dunn and Everitt, 1988; LeDoux, 2000; McGaugh et al., 1996). From an evolutionary perspective, it is clearly adaptive for memory of emotional stimuli to be enhanced, because emotional stimuli, whether pleasant or aversive, would have a greater survival value than neutral stimuli (Hamann et al., 1999). Thus, heightened cognition as a response to stress may be an adaptive mechanism enabling an organism to respond effectively to a real or potential threat to its survival. However, a stressful experience may also have adverse consequences, including deterioration in learning and memory capacity (Kim and Diamond, 2002).

The relationship between the strength of consolidation and the emotionally arousing event seems to follow an inverted U-shaped function; one important factor that determines whether there will be enhancement or impairment of memory is the level of amygdala engagement. In turn, the level of amygdala activation is a direct consequence of the characteristics of the stimulus such as intensity, duration, and so on. At moderate levels of arousal (hence of amygdala's involvement), the resulting memory will be potentiated. On the other hand, when the subject encounters neutral items (with no involvement of the amygdala) the result will be a relatively ineffective memory consolidation.

Findings from functional imaging studies in humans lend further support to a good correlation between increased activity within the amygdala during encoding, and subjects' subsequent performance on recognition or recall memory tasks. Emotionally arousing stimuli that activate the amygdala during encoding are remembered better, whereas encoding information that is emotionally neutral correlates with activation of the hippocampus, but not the amygdala (Alkire et al., 1998) and with lower level of performance in memory tasks.

When the emotional items are too immense (hence extreme involvement of the amygdala), the outcome may be memory impairment. Under conditions of high stress and amygdala activation subjects tend to show impaired attentional processes, for example, problems discriminating between relevant and irrelevant stimuli. Such impairments will easily prevent successful acquisition of useful information (Lupien and McEwen, 1997).

Accordingly, very high levels of emotional arousal may prevent the proper evaluation and categorization of experience by interfering with cognitive function (van der Kolk, 1997), and as a result some aspects of the experience may be consolidated while others may be impaired. Hence, the result of exceptional life experiences (such as flashbulb memory following important public events, or post-traumatic stress disorder (PTSD) developed following exposure to a severe trauma) may be a combination of *enhanced* and *harmed* memories (Adolphs et al., 2000).

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B. EMOTIONAL TAGGING: THE AMYGDALA ENHANCES HIPPOCAMPAL MEMORY FOLLOWING EMOTIONAL EVENTS

An emotional experience that is moderately arousing (in contrast to neutral or extremely emotional events) is suggested to activate the amygdala to promote the enhancement of cognitive or declarative memories that are emotionally loaded. During an emotional experience the amygdala interprets the emotional value of the incoming information; it attaches emotional significance to aspects of the experience and passes this evaluation on to (among other brain regions) the hippocampus (van der Kolk, 1997) which is considered central for the acquisition and consolidation of declarative memory (Eichenbaum, 1999; Maguire et al., 1999; Squire, 1992; 1998). The hippocampus puts a specific event into its proper context, it binds together multiple events that co-occur during an experience, organizes and categorizes them, and through this kind of rich processing it converts short-term into long-term memories, making possible the formation of accurate episodic memories (Chiba et al., 1994; Kesner et al., 1996). Emotional inputs from the amygdala help in sorting the more relevant from the less relevant aspects of an experience, in order to retain only the former in long-term memory. Accordingly, the intensity of the input coming from the amygdala correlates with the intensity of memory encoding in the hippocampus. Emotionally arousing events are thereby better remembered than neutral events, which are generally weakly retained or require repetition to endure (Cahill and McGaugh, 1998). It has been suggested that following an emotionally arousing event the amygdala signals to the hippocampus that an emotional experience has occurred that is worth storing; this leads to the reinforcement of consolidation of that event. The amygdala “marks” an emotionally charged experience as important, presumably by strengthening synapses located on neurons that have just been activated in another brain-memory system that is engaged in the learning situation. We termed this intensification of cognitive memory by amygdala activation “emotional tagging” (Akirav and Richter-Levin, 1999; 2002; reviewed by Richter-Levin and Akirav, 2003). Accordingly, augmenting the general arousing influence of an emotional experience is a more specific impact on memory processes, i.e., potentiating the consolidation of emotionally loaded aspects of an experience into enhanced long-term memory.

C. AMYGDALAR MEDIATION OF THE EFFECTS OF THE STRESS HORMONES ON HIPPOCAMPAL MEMORY PROCESSES

During emotional experiences stress hormones and other neurotransmitters are released, which give the event special significance and prominence in the memory pathways (Robertson, 2002).

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Naturally, multiple factors mediate stress effects on hippocampal functioning, and behavioral stress leads to the activation of a wide variety of neurotransmitters and neuroendocrine systems that can potentially affect learning and memory. These include corticotrophin-releasing factor (CRF), opioid peptides, neurosteroids, etc. (de Wied and Croiset, 1991). However, the adrenal stress hormones, norepinephrine and glucocorticoids, appear to play an important role in enabling the emotional significance of an experience to regulate the strength of its memory. The full expression of stress effects on the hippocampus seems to require co-activation of the amygdala and hippocampus, in concert with the actions of the stress hormones directly on the hippocampus.

Specifically, there is growing literature indicating that the BLA is critical for the expression of the modulatory effects of a stressful experience on hippocampal learning and memory function (Cahill and McGaugh, 1996; Kim et al., 2001; Kim and Diamond, 2002; McGaugh et al., 1996; Packard and Chen, 1999; Packard et al., 1994; Packard and Teather, 1998; Richter-Levin and Akirav, 2000; Roozendaal et al., 1999; Roozendaal et al., 1996; 1998; Shors and Mathew, 1998).

There are indications that the effects of norepinephrine and glucocorticoids (corticosterone in the rat) on hippocampal memory consolidation depend critically on the BLA, and more specifically that the BLA is a locus of action of these stress hormones in modulating memory consolidation. For example, it has been shown that post-training injections of the synthetic glucocorticoid dexamethasone enhanced the performance in a 48-h inhibitory avoidance retention test, and that a selective N-methyl-d-aspartate (NMDA)-induced lesion of the BLA blocked this enhancement (Roozendaal and McGaugh, 1996). In another task, intra-hippocampal infusions of a glucocorticoid receptors (GRs) agonist (RU 28362) given 60 min before a spatial task retention test impaired retrieval (Roozendaal et al., 2003) and a selective NMDA-induced lesion of the BLA 1 week before training blocked this impairment. Likewise, post-training microinfusions of norepinephrine or the beta-noradrenergic antagonist propranolol into the BLA immediately following training in a spatial version of the water maze task was also shown to modulate spatial performance. Retention latencies obtained on the second training day revealed that norepinephrine dose-dependently enhanced retention for the location of the hidden platform whereas propranolol significantly impaired retention (Hatfield and McGaugh, 1999). Hence, the effects of the stress hormones (either by microinfusion or following a stressful event) which are mediated by the BLA may determine whether the cognitive function will be enhancement or impairment. The stress hormones' effects on hippocampal memory processes also seem to follow an inverted U-shaped dose-response relationship: extremely low and high

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levels may impair consolidation or plasticity whereas moderate activation seems to be a prerequisite for the long-term storage of information or to its reinforcement. Thus, removal of circulating corticosteroids (via adrenalectomy) or selective mineralocorticoid receptors (MRs) or GRs antagonist injections impaired acquisition and retention in hippocampus dependent tasks, such as spatial learning, avoidance, and contextual fear conditioning. At the same time exposure to a stressor or experimentally-induced high levels of corticosterone were reported to impair acquisition and retention of those tasks (Cahill et al., 1994; Conrad et al., 1996; 1997; 1999; Diamond et al., 1994; 1996; 1999; Diamond and Rose, 1994; Oitzl and de Kloet, 1992; Oitzl et al., 1994; Pugh et al., 1997; de Quervain et al., 1998; Sandi and Rose, 1994b; Vaher et al., 1994). In contrast, intermediate increase in circulating corticosteroids has been shown to facilitate memory in different learning paradigms (Akirav et al., 2004; Akirav et al., 2001; Cordero and Sandi, 1998; Flood et al., 1978; Liu et al., 1999; Oitzl and de Kloet, 1992; Pugh et al., 1997; Sandi et al., 1997; Sandi and Rose, 1994a). A similar pattern was demonstrated with norepinephrine; retention was enhanced at moderate doses and impaired at high doses in a variety of training tasks, including inhibitory avoidance, active avoidance, discrimination learning, and appetitively motivated tasks (Gold and van Buskirk, 1975; Introini-Collison and McGaugh, 1986; Izquierdo and Dias, 1985; Liang et al., 1986; McGaugh et al., 1990).

There are several possible ways in which the BLA may be involved in mediating the stress hormones' effects on memory storage. The stress hormones can act in parallel to affect memory function through binding to receptors in the amygdala, in the hippocampus, or in other brain structures. This will activate the amygdala and the hippocampus and thereby mediate the effects of the stress hormones on memory formation. Norepinephrine may be released directly into the hippocampus and the amygdala from ascending terminals of the locus coeruleus upon arousal and stress, which in turn may induce changes (enhancement or impairment) in the neural activity engaged in memory processes (Seidenbecher et al., 1997). Stress produces increases in norepinephrine turnover in the locus coeruleus, the hippocampus, and the amygdala, as well as in the hypothalamus and the cerebral cortex (Charney et al., 1995). Glucocorticoids released by an arousing experience bind to steroid receptors in the BLA, the hippocampus, and other parts of the brain. For example, it has been suggested that glucocorticoids bind directly to GRs in the BLA and their effects may be mediated via an interaction with beta-adrenergic mechanisms in the BLA (Roozendaal, 2000). However, glucocorticoid release following an emotional experience probably also bind to GRs and MRs in the hippocampus and exert facilitative or damaging influence directly there.

D. PARAMETERS THAT MAY DEFINE THE OUTCOME OF AMYGDALA MODULATION OF HIPPOCAMPUS DEPENDENT MEMORY PROCESSES

A key question when we examine stress-memory interactions is under which conditions do the effects of amygdala activation on hippocampus dependent memory functions change from improvement to impairment of learning and memory. In this chapter we address the issue of amygdala modulation of hippocampal memory processes and demonstrate that amygdala activation may result in memory enhancement or memory impairment, and that these effects may be critically dependent on four main factors:

(1) The intensity of amygdala activation (i.e., the level of stress or amygdala direct stimulation), (2) the temporal relation between the activation of the amygdala and the hippocampus dependent memory function (i.e., the time window between amygdala and hippocampus activation), (3) the duration of amygdala activation (which is closely related to the activation of the stress hormones and whether their presence in the system is brief or lingering), and (4) the contextual input during the processing of the information.

D.1. The intensity of amygdala activation

(i) Moderate amygdala activation results in enhanced memory

Studies with humans (Bradley et al., 1992; Gallagher and Chiba, 1996; Hamann et al., 1999) and animals (Cahill and McGaugh, 1990; 1998) have demonstrated that memory is better for emotionally arousing stimuli than for emotionally neutral stimuli. It has been suggested that the amygdala may be more extensively involved in training situations that are highly arousing (Cahill and McGaugh, 1990) and that those stimuli invoking weaker emotional responses appear much less effective at consistently or robustly activating the amygdala. We have demonstrated that a highly arousing learning experience that significantly activated the amygdala also led to better hippocampus-dependent memory (Akirav et al., 2001). We examined the activation of the memory-related biochemical marker ERK2 (ERK/MAPK; extra cellular-signal regulated kinase/mitogen-activated protein kinase) in the hippocampus and the amygdala following a spatial learning task performed under different stressful conditions. We found that animals trained for a massed (1 hr of training in one day) spatial task in a water maze under cold water conditions (moderate level of stress) showed better performance in the spatial task and higher levels of corticosterone than animals trained in warm water (mild level of stress). Significant activation of ERK2 in the hippocampus was found in all the animals that had acquired the spatial task (irrespective of the level of stress involved) whereas ERK2 activation in the amygdala was found only in animals that acquired the task in cold water. Animals that were exposed to the cold water with no escape platform in the maze (hence with no spe-

cific task to learn) and showed the highest corticosterone levels did not show ERK2 activation in the amygdala, indicating that ERK2 activation in the amygdala was learning-specific. The participation of the amygdala in learning seems to be directly dependent on the training conditions; the water temperature may have acted differently on consolidation mechanisms via the influence on the amygdala during and/or following the training, and this led to differential performance in the test. Indeed, the activation of the amygdala (as seen by the activation of ERK2) following the emotionally charged hippocampus-dependent learning experience apparently led to the better performance of the cold-water trained rats in the spatial task (Akirav et al., 2001).

These ideas win support from another set of studies that demonstrated the inverted U-shaped curve between arousal and performance: rats trained at 19°C showed better performance in the retention test than rats trained at 25°C (Sandi et al., 1997) whereas rats trained at 12°C showed impaired performance and significantly higher corticosterone levels than rats trained at 26°C or 19°C (Sandi et al., 1997; Selden et al., 1990).

Note that the increase in corticosterone levels is probably not a sufficient condition to mediate stress effects on hippocampal plasticity and learning. Specifically, an intact amygdala is necessary for the expression of the modulatory effects of stress and stress-related hormones on hippocampal long-term potentiation (LTP) and memory. Lesions in the amygdala block the modulatory effects of systemic and post-training intra-hippocampal injections of stress hormones on long-term memory assessed in a variety of learning tasks, including inhibitory avoidance, Y-maze discrimination, and water-maze tasks (Cahill and McGaugh, 1990; Packard and Chen, 1999; Roozendaal and McGaugh, 1996; Roozendaal et al., 1996; 1998). Moreover, a recent study has shown that amygdala lesion effectively blocked stress effects on hippocampal LTP and spatial memory without significantly affecting the increase in corticosterone secretion in response to stress (Kim et al., 2001).

(ii) Extreme amygdala activation results in enhanced and impaired memory

Two interesting phenomena, PTSD and flashbulb memories, are important examples of how extraordinary amygdala activation can result in a combination of enhancement and impairment of memory.

Extremely high arousal and stress levels may lead to pathological conditions. During excessive cases of stress, the augmentation of the stress hormones activation or their long-term presence in the system may underlie the high anxiety levels and the repetitive reliving of the stress experience (or traumatic event), which may well result in disturbances such as PTSD. Studies of PTSD suggest a specific association between the extreme stress of a trauma and alterations in memory functioning (Bremner, 1999; Pitman, 1989). In general, two types of memory disturbances have been identified in traumatized individuals: intrusive memo-

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ries and impoverished memory functioning. Intrusive memories may be experienced as reenactments of the original trauma ('flashbacks') whereas the poor memory may be evident in deficits in declarative memory, fragmentation of memories, and trauma-related amnesia (Elzinga and Bremner, 2002). The coupling of the amplification of memory for a traumatic stimulus with the decrement in memory for surrounding contextual material is indeed intriguing. It has been proposed that the failure to consolidate material proximate to the traumatic stimulus (for example, the context of the trauma) is due to amygdala suppression of hippocampal function, and that the enhancement of memory at the highest levels of emotional arousal is because the amygdala then becomes the exclusive locus of consolidation of the traumatic event (Layton and Krikorian, 2002). Similarly, it has been suggested that under certain stressful conditions hippocampal functioning is impaired while amygdala processing is heightened (Metcalf and Jacobs, 1998), so emotional memory storage in the amygdala will be facilitated at the expense of hippocampus-dependent spatio-temporal processing (Diamond et al., 2001).

Interesting support for these ideas from animal studies has been presented in a recent study by Vouimba et al. (2004; also see Yaniv et al., 2003). They showed that in freely behaving rats, exposure to an acute inescapable stressful experience (30 min on a platform) *facilitated* LTP in the basal amygdaloid nucleus following entorhinal cortex stimulation. In another study the exposure to this stressful experience was found to *inhibit* LTP in the CA1 area of the hippocampus and in the amygdala-medial prefrontal cortex pathway (Maroun and Richter-Levin, 2003). It seems that under conditions of heightened emotionality the induction and maintenance of hippocampal synaptic plasticity are impaired and the induction of amygdaloid synaptic plasticity is enhanced. A possible explanation for this may be that under stressful conditions it is essential to "block" the high-order behavior mediated by the hippocampus (and the prefrontal cortex) and to allow more automatic responses that are dependent on subcortical areas such as the amygdala (Diamond et al., 2001).

Another example of an intense emotional event is seen in flashbulb memories. The vividness with which an event is recalled strongly correlates with the emotionality of the event at the time it occurred, and flashbulb memories seem to represent the extreme of this affect-vividness relationship (Reisberg and Heuer, 1992).

Flashbulb memories are long-lasting memories for the context of an important public event, namely experiences occurring both shortly before and shortly after the event (Brown and Kulik, 1977). These memories are probably triggered by emotional factors (intensity of emotional feeling, appraisal of the original event) and by social factors (social sharing of the news, following media debate about the event) (Curci et al., 2001).

Emotion seems to cause selectivity in memory, presumably as a result of selectivity in both encoding and post-event elaboration. Physiological arousal may lead to a narrowing of attention during emotional events; hence, the emotion promotes memory for materials tied to an event's center, and works against memory for materials at the event's edge (i.e., pulling attention away from remote details) (Reisberg and Heuer, 1992). This may result in a potentiated memory of some aspects of the event (gist) but impaired memory of other of its details. This notion gains some support from studies with amygdala or hippocampus damaged patients (Adolphs et al., 2001; Hamann et al., 1997). For example, it has been shown that bilateral, but not unilateral, damage to the amygdala resulted in poorer long-term memory for gist but superior memory for visual details of aversive and neutral scenes (Adolphs et al., 2001). Additionally, although flashbulb memories are more extensive, more consistent, and reported with more confidence than other memories, they are not perfect. There seems to be a higher probability of recalling the personal context of the discovery of shocking news than the news itself (Bohannon and Symons, 1992).

All in all, the emotional nature of stimuli seems to have a complex influence on long-term declarative memory for those stimuli: whereas emotion enhances memory for gist, it may suppress memory for details (Adolphs et al., 2001).

D.2. The temporal relation between the activation of the amygdala and the hippocampus-dependent memory function

To examine the neural bases of amygdala modulation of hippocampal long-term memory we looked at long-term potentiation (LTP) of synaptic transmission in the hippocampal dentate gyrus (DG) area as a function of amygdala activation. LTP is the most widely studied cellular model for synaptic plasticity, and long-lasting alterations in synaptic plasticity are considered to be involved in memory formation.

We wanted to determine the possible influence of activating both the amygdala and the hippocampus within a narrow (30 sec; priming) or a spaced (1-2 hrs) time window to examine how it may contribute to long-term functional changes during memory formation. We have shown (Akirav and Richter-Levin, 1999; 2002) that BLA stimulation within a narrow time window before perforant path (PP) tetanization resulted in the enhancement of DG - LTP whereas BLA stimulation 1 or 2 hrs prior to PP activation resulted in the suppression of hippocampal LTP. Moreover, we found that whereas a stressful experience suppresses hippocampal LTP, priming the BLA in stressed animals relieves the depressant effect of behavioral stress on hippocampal LTP (Akirav and Richter-Levin, 1999). This study strongly supports the notion that the amygdala and the hippocampus may act synergistically to form long-term memories of signifi-

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cantly emotional events, and that the temporal relationship between the activation of the amygdala and the hippocampus may be critical to the outcome. More support for these ideas comes from two studies that examined the influence of amygdala activation on hippocampal LTP. Frey et al., (2001) showed that temporally correlated stimulation of the BLA and the PP can enhance the maintenance of DG-LTP. This form of heterosynaptic plasticity occurs on a weak decaying form of LTP, is optimal when co-stimulation is applied within a narrow time window (5-15 minutes), involves muscarinic and β -adrenergic receptors, and depends on *de novo* protein biosynthesis. Pape and Stork (2003) suggest that temporally correlated electrical activity in amygdaloid and hippocampal networks, such as occurs, for instance, during theta waves, may facilitate this heterosynaptic plasticity.

Furthermore, Seidenbecher et al., (1997) showed that LTP in the DG of freely moving rats was reinforced after its induction by appetitive or aversive stimuli (which are known to activate the amygdala). The efficacy of these stimuli terminated about 1 h after tetanization, probably reflecting time constants of the mechanisms underlying consolidation.

D.3. The duration of amygdala activation

The response to emotional or stressful experiences involves biphasic secretion of the stress hormones in which norepinephrine represents the first phase and glucocorticoids represent the second phase. The potent effects of the stress hormones on learning and brain plasticity are presumably mediated by influences involving the amygdala (Cahill and McGaugh, 1998; Liang et al., 1990; McGaugh, 2000; Roozendaal and McGaugh, 1996). Norepinephrine has been shown repeatedly to be involved in memory reinforcement of different behavioral tasks (Cahill et al., 1994; McGaugh, 1989) and in the reinforcement of hippocampal LTP (Izquierdo and Medina, 1995; Seidenbecher et al., 1997). Specifically, it has been suggested that noradrenergic activation of the BLA may serve to modulate memory storage and plasticity in the hippocampus (Ferry et al., 1999; Frey et al., 2001; Ikegaya et al., 1997).

The glucocorticoids have dose-dependent inverted U-shaped effects on hippocampal LTP and memory (Kerr et al., 1994; Pavlides et al., 1993; 1995). It has been suggested that a functioning BLA is required for adrenal steroids to exert their influence on hippocampal memory storage (Roozendaal et al., 1996; 1999; Roozendaal and McGaugh, 1997).

In view of this, we hypothesized that norepinephrine is the main mediator of the BLA rapid enhancing effect on hippocampal LTP and that corticosterone mediates the BLA slower suppressive effect. However, we found that the effects of *both* the priming and the spaced activation of the BLA on hippocampal plasticity were mediated by norepinephrine and corticosterone (Akirav and Richter-Levin, 2002). Because both neuromodulators seem to be involved in the enhancing as well as the depress-

ing effects of the BLA, a third factor must be postulated that will define whether an enhancement or inhibition of plasticity will take place. One factor may be the duration of the stress hormones' presence in the system. Therefore, the effects of a brief exposure to these hormones may be excitatory, whereas their prolonged presence in the spaced phase may lead to the inhibitory effect. Hence, at the onset of an emotional event the stress hormones may permissively mediate plasticity and lead to its facilitation whereas their prolonged presence in the system may suppress the cognitive response to stress.

These ideas are supported by studies showing that the duration of corticosteroid action may be an important factor in the control of learning and memory (Oitzl et al., 1998). It has been shown that whereas intermediate duration of corticosterone treatment or stress facilitated learning (Luine et al., 1996; Shors et al., 1992), exposure to chronic stress or corticosterone treatment significantly impaired memory (Bodnoff et al., 1995; Conrad et al., 1996; Dachir et al., 1993; Luine et al., 1996). For example, in their study Vouimba et al., (submitted) showed that whereas exposure to acute stress facilitated LTP in the entorhinal-basal amygdaloid nucleus pathway, the exposure to a repeated stressor inhibited LTP in the DG and inhibited long-lasting LTP (> 3 days) in the basal amygdaloid nucleus. Furthermore, animals exposed to the repeated stress showed higher levels of immobility than animals exposed to the acute stressor.

D.4. The contextual input during the processing of information

Another factor that may determine amygdala-mediated cognitive performance is the contextual input during the various stages of information processing. The release of corticosterone in our water maze experiment (hence the activation of MRs and GRs; Akirav et al., 2001) was within the context of the learning situation and seemed to be essential for the consolidation of the learned information (Joels, 2001). Similarly, when corticosterone was injected immediately following training for a spatial task in the water maze, performance in the task improved (Sandi et al., 1997). However, when a lower dose of corticosterone was injected prior to the retrieval test, performance in the task declined (de Quervain et al., 1998). Thus, in addition to the amount of corticosterone, the temporal relationship between GR activation and the behavioral task is important (de Kloet et al., 2002; Oitzl et al., 1997; 1998). In different hippocampus-dependent tasks, the exposure to an unrelated stressor (e.g., foot shock, exposure to an unfamiliar environment, etc.) interrupted the performance in the learning task (Diamond et al., 1996; de Quervain et al., 1998). It has been suggested that although GRs are necessary for consolidation of information, subsequent GR activation, when triggered by a distracting stressor that is out of the context with respect to the original learning task, disrupts ongoing consolidation and apparently influences retrieval of previously stored information (de Kloet et al., 1999).

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To summarize, exposure to stressors, and as a result activating the amygdala and the release of the stress hormones out of the context of the original learning task, may apparently lead to a completely different behavioral performance than exposure to stressors that are within the context of the learning experience.

E. SUMMARY

The amygdala is necessary for the final memory seen with highly aversive, emotionally arousing experiences. The exposure to a threatening or stressful experience may result in increased motivation and arousal that may facilitate cognition. Yet, it may also have a harmful effect on the organism's cognition function and may enhance its susceptibility to disease.

Direct manipulations of neural activity in the amygdala (e.g., with electrophysiological stimulation) or indirect manipulations (with exposure to behavioral stressors) have shown that the amygdala, using the stress hormones, exerts a modulatory effect on the hippocampus, which is directly involved in declarative memory consolidation.

It seems that the behavioral expression of emotionally motivated learning depends on the involvement of the amygdala during a narrow and highly specific time window (Bianchin et al., 1999; Cahill and McGaugh, 1998). Factors such as the intensity of the experience (which may range from neutral to extremely strong) and the duration of the stress hormones' presence in the system (e.g., in an acute versus repeated stress experience) may significantly determine the consequence of amygdala influence on the consolidation of emotionally charged experiences.

ACKNOWLEDGMENTS

This research was supported by The Israel Science Foundation – The Charles H. Revson Foundation (no.582/00-1 to G.R-L.).

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